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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/593,316	06/13/2000	John Clark	730/002	5627

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EXAMINER

LI, QIAN J

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 01/30/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/593,316

Applicant(s)

CLARK ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 13-17, 22 and 27-37 is/are pending in the application.
- 4a) Of the above claim(s) 7, 13-17, 22 and 27-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 33-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 June 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 16. 6) ☐ Other: _____

DETAILED ACTION

The Response filed November 21, 2002 has been entered and assigned as Paper #15. Claims 1-7, 13-17, 22, and 27-37 are pending in the application, claims 1-6 and 33-37 are under current examination.

This application contains claims (7, 13-17, 22, 27-32) drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 1-6 and 33-37 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on Paper Nos: 7 and 12, and the following.

Applicant's arguments have been fully considered, but found not persuasive. They will be addressed point-by-point as following.

With respect to the argument that sheep cells having an inactivated $\alpha(1,3)$ galactosyltransferase allele can readily be produced, applicants argue that the specification provides for the first time the sequence for sheep $\alpha 1,3$ GT, and steps

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regarding how to make a sheep having an inactivated $\alpha 1,3$ GT gene. Applicants further argue that it is not necessary to target exon 8 or 9 to practice the claimed invention.

Applicants also cite art of record to prove the point.

In response, the concerns raised in the previous Office actions are not whether the steps of making a sheep having an inactivated $\alpha 1,3$ GT gene are known or feasible, the concerns are whether a sheep with the desired phenotype are generated and whether applicants are in possession of the claimed invention at the time the application was filed. Claims are drawn to ovine tissue devoid of antibody-detectable Gal $\alpha (1,3)$ Gal determinants or an ovine animal homozygous for inactivation of a $\alpha 1,3$ GT gene. However, the specification only provides a fetus with a heterologous inactivation of $\alpha 1,3$ GT gene. Even if the fetus could be brought to term healthy, a heterozygous $\alpha 1,3$ GT knockout sheep is not "an ovine animal homozygous for inactivation of an $\alpha 1,3$ GT gene", and the tissue from such sheep would have antibody-detectable Gal $\alpha (1,3)$ Gal determinants. Thus, the specification fails to provide a proper description for what is claimed.

With respect to the argument that animals having an inactivated $\alpha (1,3)$ GT allele can readily be made from inactivated donor cells by nuclear transfer. Applicants argue that the technique has been used for creating Dolly the sheep, and there is no reason to believe that genetically altering the donor cell would affect its suitability as a nuclear donor, and that several publications confirmed the fact. Applicants particularly point to the Lai et al and Dai et al references, because they illustrated that $\alpha (1,3)$ GT knockouts

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can readily made in another ungulate species by the possession of the corresponding α (1,3)GT gene.

In response, both Lai and Dai et al reported a knockout pig that is heterozygous for α (1,3)GT gene, i.e. only one allele of the α (1,3)GT gene is disrupted. The pig is not a homozygous inactivation for α (1,3)GT gene as presently claimed.

With respect to the argument that animals that are homozygous for inactivated α (1,3)GT gene can readily be produced. Applicants argue that homozygous animals can be made by interbreeding heterozygous knockout animals, thus, the only relevant question is whether knocking out both α (1,3)GT alleles would somehow compromise the viability of the animal. The applicants further cite US 5,849,991 patent disclosing homozygous α (1,3)GT knockout mice as proof of feasibility for a homozygous α (1,3)GT knockout sheep.

In response, viability of the homozygous knockout α (1,3)GT is only one of the many concerns and relevant questions. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), this is particularly true in the art of transgenic animals with respect to transgene behavior and resulting phenotype. Art of record acknowledges that it is unpredictable how genetic make-up would influence the transgene behavior (*Linder*).

Regarding the new citation of US 5,849,991 patent and the new issue raised accordingly in Paper #15, it is unpredictable from the phenotype of a mouse to that of a large animal. *Hammer et al* (J Anim Sci 1986;63:269-78) report the production of

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transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). *Mullins et al.* (J Clin Invest 1996 Apr;97:1557-60) state "A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER" (page 1559, Summary). *Wall et al* (J Dairy Sci 1997;80:2213-24) further report that "TRANSGENE EXPRESSION AND THE PHYSIOLOGICAL CONSEQUENCES OF TRANSGENE PRODUCTS IN LIVESTOCK ARE NOT ALWAYS PREDICTED IN TRANSGENIC MOUSE STUDIES" (page 2215, first paragraph). Without evidence to the contrary, transgene expression as well as knockouts phenotype in different species of genetically engineered animals is not consistent and varies according to the particular host's genetic background. If applicants still believe that mouse and sheep are equivalent in the phenotype of the $\alpha(1,3)$ GT knockouts, then, US 5,849,991 patent may become available as prior art under section 103.

With respect to the argument that cells from homozygous knockout animals will have cells and tissues devoid of the Gala(1,3)Gal xenoantigen.

Applicants again cite US 5,849,991 patent to support the argument, however, as indicated in the immediate preceding section, the phenotype of a $\alpha(1,3)$ GT knockout sheep could not be reasonably predicted from the phenotype of a mouse, and so far, the specification fails to provide an adequate description to support the full scope of the claims.

Accordingly for reasons of record and those set forth above, the instant specification fails to meet the written description requirement for the broad scope of the claims.

ENABLEMENT REQUIREMENT

Claims 1-6 and 33-37 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in paper Nos: 7 and 12, and those given in the immediate foregoing sections. Because the specification contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation, since a disclosure cannot teach one to make or use something that has not been fully described.

In paper #15, applicants' responses to previous Written Description and Enablement rejections are combined and have been addressed in the foregoing section.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *homozygous inactivation of α 1,3GT gene* in an ovine animal, in particular for obtaining ovine tissue devoid of antibody-detectable Gal α (1,3)Gal determinants, the lack of guidance provided by the specification as well as the absence of working examples with regard to homozygous inactivation of α 1,3GT gene in an ovine animal, and the breadth of the claims directed to the use of numerous means to abolishing Gal α (1,3)Gal determinants in any ovine animal, it would have

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required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 27, 2003

ANNE M. JOSEPH, D.
PRIMARIAL EXAMINER

